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Original article

Coffee consumption, genetic susceptibility and risk of latent autoimmune diabetes in adults: A population-based case-control study

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ABSTRACT

Aim. – Coffee consumption is inversely related to risk of type 2 diabetes (T2D). In contrast, an increased risk of latent autoimmune diabetes in adults (LADA) has been reported in heavy coffee consumers, primarily in a subgroup with stronger autoimmune characteristics. Our study aimed to investigate whether coffee consumption interacts with HLA genotypes in relation to risk of LADA.
Methods. – This population-based study comprised incident cases of LADA ($n = 484$) and T2D ($n = 1609$), and also 885 healthy controls. Information on coffee consumption was collected by food frequency questionnaire. Odds ratios (ORs) with 95% CIs of diabetes were calculated and adjusted for age, gender, BMI, education level, smoking and alcohol intake. Potential interactions between coffee consumption and high-risk HLA genotypes were calculated by attributable proportion (AP) due to interaction.
Results. – Coffee intake was positively associated with LADA in carriers of high-risk HLA genotypes (OR: 1.14 per cup/day, 95% CI: 1.02–1.28), whereas no association was observed in non-carriers (OR: 1.04, 95% CI: 0.93–1.17). Subjects with both heavy coffee consumption (≥ 4 cups/day) and high-risk HLA genotypes had an OR of 5.74 (95% CI: 3.34–9.88) with an estimated AP of 0.36 (95% CI: 0.01–0.71; $P = 0.04370$).
Conclusion. – Our findings suggest that coffee consumption interacts with HLA to promote LADA.

Introduction

Observational studies have consistently shown that coffee consumption is associated with a reduced risk of type 2 diabetes (T2D) [1]. The potentially protective effect has been attributed to improvement of insulin sensitivity and glucose metabolism [2–4], and reduced oxidative stress [5]. In contrast, an increased risk of latent autoimmune diabetes in adults (LADA) was recently observed in heavy consumers of coffee [6], although the excess risk was only apparent for LADA patients with high levels of glutamic acid decarboxylase antibodies (GADA). Indeed, a positive association between coffee intake and levels of GADA has been observed [6].

Such a finding suggests that coffee either triggers or promotes islet autoimmunity. This fits with findings in adolescents with type 1 diabetes (T1D), and is also consistent with data on per capita coffee consumption across different countries and incidence of T1D [7,8]. However, those studies were hampered by small numbers [8] and crude data [7]. Nevertheless, the impact of coffee intake on the immune system and autoimmune diseases has been receiving

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increasing attention [9], and high intakes have been linked to an increased risk of rheumatoid arthritis [10] as well as a reduced risk of multiple sclerosis [11].

Human leucocyte antigen (HLA) haplotypes are strongly linked to the development of autoimmune diabetes [12,13]. Autoimmune diabetes-related HLA haplotypes are found in about 90% of children with T1D [14], in 70% of patients with adult-onset autoimmune diabetes [15] and in 37–53% of the general Caucasian population [16,17]. However, as not all genetically susceptible individuals develop autoimmune diabetes, environmental factors are likely to be important in the initiation and/or progression of disease [18]. Yet, whether coffee intake interacts with HLA genotypes has not been previously explored. Thus, the aim of the present study was to investigate the risk of LADA in relation to coffee intake, using newly collected data from the same population as in our previous study [6], but with almost twice as many cases and including information on HLA genotypes associated with autoimmunity [12–15].

Subjects and methods

Study population and design

The study was based on the Epidemiological Study of Risk Factors for LADA and Type 2 Diabetes (ESTRID), a Swedish population-based case-control study. Details of ESTRID have been described elsewhere [6]. In short, ESTRID is a substudy of the All New Diabetics in Scania (ANDIS) study (http://andis.ludc.med.lu.se/) [19], an extensive study aimed at characterizing all new cases of diabetes in southern Sweden. Since 2010, all newly diagnosed patients with LADA have been invited to enrol in ESTRID. In 2012, recruitment was expanded to All New Diabetics in Uppsala (ANDIU; www.andiu.se/), a sister study to ANDIS in the county of Uppsala (in the middle of Sweden). For each identified LADA patient, four incident cases of T2D were randomly selected from ANDIS/ANDIU and matched by date of participation.

Of the enrolled patients, 95% came from Scania and 5% from Uppsala, for whom questionnaire and clinical and genetic information was collected. Also, controls without diabetes ($\geq$ 35 years of age, $n = 1909$) were randomly selected from the national population register, which supplied questionnaire information, although no blood samples were taken. For purposes of the present study, data from population-based, randomly selected, controls recruited from a sister study of rheumatoid arthritis, the Epidemiological Investigation of Rheumatoid Arthritis (EIRA) [20], were included. EIRA was carried out in the middle and southern parts of Sweden according to a similar methodology as in ESTRID, but with genetic information available.

The analytical sample for the present study comprised all patients [LADA: $n = 484$ (465 from ANDIS, 19 from ANDIU); T2D: $n = 1609$ (1519 from ANDIS, 90 from ANDIU)] included in ESTRID from 2010 up to July 2017, with complete information on coffee consumption and potential confounders, together with all controls from EIRA, recruited from 2005 to 2009, with complete information on coffee consumption, confounders and HLA genotypes ($n = 885$). Of the cases, 48% were from our previous paper, which was based on cases collected during 2010–2013 [6]. Ethics approvals for both ESTRID and EIRA were obtained from the relevant ethics committees in Stockholm, and all participants gave their informed consent.

Coffee consumption and covariates

At the time of recruitment, patients (ESTRID) and controls (ESTRID and EIRA) answered an extensive questionnaire that was identical as regards many items, including physical activity, education and smoking, as well as a validated [21] food frequency questionnaire (FFQ). Participants were asked to report their average daily or weekly intake of coffee (brewed coffee, boiled coffee and espresso, each type separately) over the past year. Diabetes patients received the questionnaire soon after their diagnosis and were specifically instructed to report their average intakes for the year prior to diagnosis. While there was no question regarding decaffeinated coffee, in Sweden, brewed coffee is the most common type [22], accounting for 91% of the total coffee intake in our study population, and consumption of decaffeinated coffee is highly unusual [22].

Total daily coffee intake was calculated as the sum of coffee consumption in number of cups (150 mL) per day. Also, the nutrient intake of each food item in the FFQ was estimated by multiplying frequency of consumption by nutrient content as per the Swedish National Food Agency Database [23], taking into account age-specific portion sizes [24]. Total energy intakes (kcal/day) were also calculated. Body mass index (BMI) was self-reported, and calculated as weight (in kg) divided by the square of height (in m). Average alcohol intakes were categorized as none, 0.1–4.9, 5–14.9 or $\geq$ 15 g/day. Subjects were categorized into current, former and never smokers. Highest achieved level of education was categorized into three levels: low (primary school); medium (upper secondary school); and high (university). Physical activity was assessed by validated questions [25] about average leisure-time physical activity during the preceding year with four response options, ranging from sedentary to very active.

Definition of diabetes subtypes

At the time of diagnosis, blood samples were drawn from all patients, and analyzed for GADA by enzyme-linked immunosorbent assay (Elisa) [26] and for C-peptide by the IMMULITE 2000 immunoassay system (Siemens Healthcare GmbH, Erlangen, Germany) or by cobas 6000 e601 immunology analyzer (Roche Diagnostics, Basel, Switzerland) [27]. In ANDIS and ANDIU, patients aged $\geq$ 35 years at diabetes onset were classified as either LADA if they were GADA-positive ($\geq$ 10 IU/mL) with C-peptide $\geq$ 0.2 nmol/L (IMMULITE)/or $\geq$ 0.3 nmol/L (cobas), or as T2D if they were GADA-negative ($<$ 10 IU/mL) with C-peptide $>$ 0.6 nmol/L (IMMULITE)/or $>$ 0.72 nmol/L (cobas). C-peptide criteria in the definition of T2D excludes those with relative insulin deficiency according to the definitions used in ANDIS/ANDIU [28]. At a GADA cut-off of 10.7 IU/mL, sensitivity was 84% and specificity was 98% [26]. LADA patients were also stratified according to median GADA levels ($<$ 233 and $\geq$ 233 IU/mL) into $LADA_{low}$ and $LADA_{high}$, respectively. Homoeostasis model assessment to approximate insulin resistance (HOMA-IR) and to estimate β-cell function (HOMA-β) were calculated based on fasting plasma glucose and C-peptide [29].

Genetic analysis

At the Lund University Diabetes Centre, DNA was extracted from blood samples taken of all study patients and analyzed for $>$ 300 different gene variants, using iPLEX Gold genotyping technology (Sequenom, San Diego, CA, USA). Controls from EIRA were genotyped for single-nucleotide polymorphisms (SNPs) using the Infinium Illumina 300K immunochip custom array (Illumina, San Diego, CA, USA) [30]. The focus was on carriers of high-risk HLA class-II *DR/DQ* genotypes, known to be associated with autoimmune diabetes [12]. Three SNPs in the major histocompatibility complex (MHC) region (rs3104413, rs2854275, rs9273363), shown to predict high-risk HLA *DR/DQ* genotypes relevant to autoimmune diabetes with an overall accuracy of 99.3% [31], were available in both ESTRID and EIRA. Combinations of these three SNPs were used to define HLA genotypes *DR3/4*, *DR3/3*, *DR4/4*, *DR3/X*, *DR4/X*, *DR4-DQ7*, *DR4/3-DQ8*, *DR4-DQ8*, *DRX/X* and *DQA1*0501-DQB1*020*. Genetic information was available for 83% of LADA and 80% of T2D patients. Based on the prevalence of HLA risk genotypes (Table S1; see supplementary materials associated with this article online) in our study population and on previous knowledge [14,15], subjects were categorized into high-risk HLA genotypes (*DR4-DQ8*, *DR4/3-DQ8*, *DR3/4*, *DR3/3*, *DR4/4*, *DQA1*0501-DQB1*0201*) [14,15,32,33] and other HLA genotypes (*DR3/X*, *DR4/X*, *DR4-DQ7*, *DRX/X*) [32,34].

Statistical analysis

Characteristics of the participants were expressed as means, proportions and medians (when data were skewed or influenced by outliers). Two-tailed *P* values were calculated using Chi^2 (proportions), Student's *t* (means) and Kruskal–Wallis H (medians) tests. Odds ratios (ORs) and 95% confidence intervals (CIs) for the association between coffee consumption and LADA or T2D were calculated by conditional logistic regression. An association was considered significant if the 95% CI for an OR did not include the null value of 1, which corresponds to a *P* value < 0.05 based on a two-tailed test. In all analyses unless otherwise stated, controls from EIRA were used and post-matched to ESTRID cases by age and gender [35]. Coffee consumption was analyzed as continuous (cup/day) and categorical variables. ORs of LADA and T2D were estimated in relation to HLA genotypes, and stratified in analyses by HLA genotype. The potential interaction between heavy coffee consumption and high-risk HLA genotypes was defined as any departure from the additivity of effects [36], and evaluated by calculating the attributable proportion (AP) due to interaction together with a 95% CI [37]. All analyses were conditioned on age and gender, and adjusted for BMI, alcohol consumption, smoking status and education level unless otherwise specified. Further adjustments for physical activity and total energy intakes did not change the ORs (< 10%). All analyses were done with SAS version 9.4 software (SAS Institute, Cary, NC, USA).

Results

Participants' characteristics

Mean age was 63 years in T2D patients, 59 years in LADA patients and 57 years in controls (Table 1). Compared with T2D patients, those with LADA were leaner, younger, less likely to be sedentary and of low education, but more likely to be treated with insulin, and to have lower HOMA-β and HOMA-IR scores. High-risk HLA genotypes were carried by 61% of LADA, 31% of T2D patients and 32% of controls (Table 1), and were more prevalent in $LADA_{high}$ (68%) than in $LADA_{low}$ (54%) patients (Table S2; see supplementary materials associated with this article online).

Comparison of the characteristics of EIRA controls (in the present study) and controls collected from ESTRID (with no genetic information) indicated they were similar with regard to many characteristics (Table S3; see supplementary materials associated with this article online). However, EIRA controls were younger and, as a factor of study design, a greater number were female (rheumatoid arthritis is more common in women) [20]. Differences in age and gender were handled by post-matching.

Coffee consumption, T2D and LADA

There was a tendency towards an inverse relationship between daily amounts of consumed coffee and T2D (Table 2): the OR for every additional cup/day of coffee was estimated as 0.94 (95% CI: 0.89–1.00). Results were similar when the internal controls from ESTRID were analyzed (OR: 0.92, 95% CI: 0.88–0.96 per cup/day). However, overall coffee consumption was unrelated to LADA (OR: 1.05, 95% CI: 0.98–1.13 per cup/day; Table 2). Yet, stratifying participants by HLA risk genotype revealed an association between coffee consumption and LADA among carriers of high-risk HLA genotypes (OR: 1.14 per cup/day, 95% CI: 1.02–1.28), whereas no such association was seen among non-carriers (Table 2). Moreover, the results were consistent when internal controls from ESTRID (no genetic information) were used, and LADA cases were stratified by HLA genotype (Table S4; see supplementary materials associated with this article online). Stratification of LADA patients by median GADA levels (< 233 and ≥ 233 IU/mL) indicated that coffee intake was associated with $LADA_{high}$ (OR: 1.10 per cup/day, 95% CI: 1.01–1.20), but not with $LADA_{low}$ (Table S5; see supplementary materials associated with this article online).

Interaction between coffee consumption and HLA genotype

Carriers of high-risk HLA genotypes who were heavy consumers of coffee (≥ 4 cups/day) had an OR of 5.74 (95% CI: 3.34–9.88) for LADA compared with non-carriers with low coffee consumption (< 2 cups/day; Fig. 1). Also, there was an additive interaction

Table 1
Characteristics of study participants with type 2 diabetes (T2D), latent autoimmune diabetes in adults (LADA) and controls.

Characteristics	Controls	T2D	LADA	*P*[a]
Subjects, *n*	885	1609	484	
Age, mean years (SD)	57 (9)	63 (10)	59 (12)	< 0.0001
Men, *n* (%)	239 (27)	983 (61)	259 (53)	0.0031
Low education level, *n* (%)	221 (25)	583 (36)	135 (28)	0.0007
BMI, mean kg/m² (SD)	25.5 (4.2)	31.1 (5.4)	28.1 (5.5)	< 0.0001
Physically inactive, *n* (%)	115 (13)	380 (24)	82 (17)	0.0026
Current smokers, *n* (%)	171 (19)	325 (20)	111 (23)	0.7872
Low alcohol drinkers (< 5 g/day), *n* (%)	341 (38)	823 (51)	230 (48)	0.1621
Insulin treatment, *n* (%)[b]	–	91 (6)	206 (44)	< 0.0001
C-peptide, median nmol/L (IQR)[b]	–	1.20 (0.95–1.60)	0.69 (0.43–1.13)	< 0.0001
HOMA-IR, median (IQR)[b]	–	3.6 (2.7–4.8)	2.8 (1.8–4.4)	< 0.0001
HOMA-β, median (IQR)[b]	–	69 (43–94)	38 (14–68)	< 0.0001
GADA, median IU/mL (IQR)[b]	–	–	233 (28–250)	–
HbA1c, median mmol/mol (IQR)[b]	–	51 (45–69)	64 (49–97)	< 0.0001
HLA high-risk genotype, *n* (%)[c]	280 (32)	400 (31)	243 (61)	< 0.0001

BMI: body mass index; IQR: interquartile range; HOMA-IR/β: homoeostasis model assessment of insulin resistance/β-cell function; GADA: glutamic acid decarboxylase antibodies; HLA: human leucocyte antigen.
[a] LADA vs. T2D patients.
[b] Data only available for T2D and LADA patients.
[c] Those with DR4-DQ8, DR3/4, DR3/3, DR4/4, DR4/3-DQ8, DQA1*0501-DQB1*0201 (other HLA genotypes: DR3/X, DR4/X, DR4-DQ7, DRX/X).

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Table 2
OR of LADA and type 2 diabetes in relation to coffee consumption.

	Type 2 diabetes				LADA							
					Overall			Individuals with other HLA genotype[a]		Individuals with high risk HLA genotype[a]	
	No. controls	No. cases	OR[b] (95% CI)	OR[c] (95% CI)	No. cases	OR[b] (95% CI)	OR[c] (95% CI)	Cases/controls	OR[c] (95% CI)	Cases/controls	OR[c] (95% CI)
Daily coffee consumption											
< 2 cups	198	416	Reference	Reference	108	Reference	Reference	33/137	Reference	51/61	Reference
2–3 cups	406	650	0.66 (0.52–0.84)	0.73 (0.55–0.97)	192	0.89 (0.65–1.21)	1.01 (0.73–1.40)	69/279	1.21 (0.72–2.02)	88/127	1.11 (0.65–1.95)
4–5 cups	223	368	0.69 (0.53–0.90)	0.68 (0.49–0.94)	122	0.95 (0.67–1.35)	1.06 (0.73–1.53)	41/149	1.15 (0.64–2.05)	68/74	1.43 (0.79–2.57)
≥ 6 cups	58	175	1.07 (0.74–1.56)	0.86 (0.54–1.36)	62	1.57 (0.98–2.52)	1.53 (0.92–2.52)	15/40	1.10 (0.48–2.53)	36/18	2.45 (1.12–5.35)
Per cup/day	885	1609	0.98 (0.93–1.03)	0.94 (0.89–1.00)	484	1.05 (0.98–1.13)	1.05 (0.98–1.13)	158/605	1.02 (0.93–1.12)	243/280	1.10 (1.01–1.20)

[a] High risk HLA genotype: Individuals with *DR4-DQ8*, *DR3/4*, *DR3/3*, *DR4/4*, *DR4/3-DQ8*, and *DQA1*0501-DQB1*0201*; Other HLA genotypes: individuals with *DR3/X*, *DR4/X*, *DR4-DQ7*, and *DRX/X*.
[b] Conditioned on age, gender.
[c] Conditioned on age and sex, and adjusted for smoking, BMI, education, and alcohol consumption.

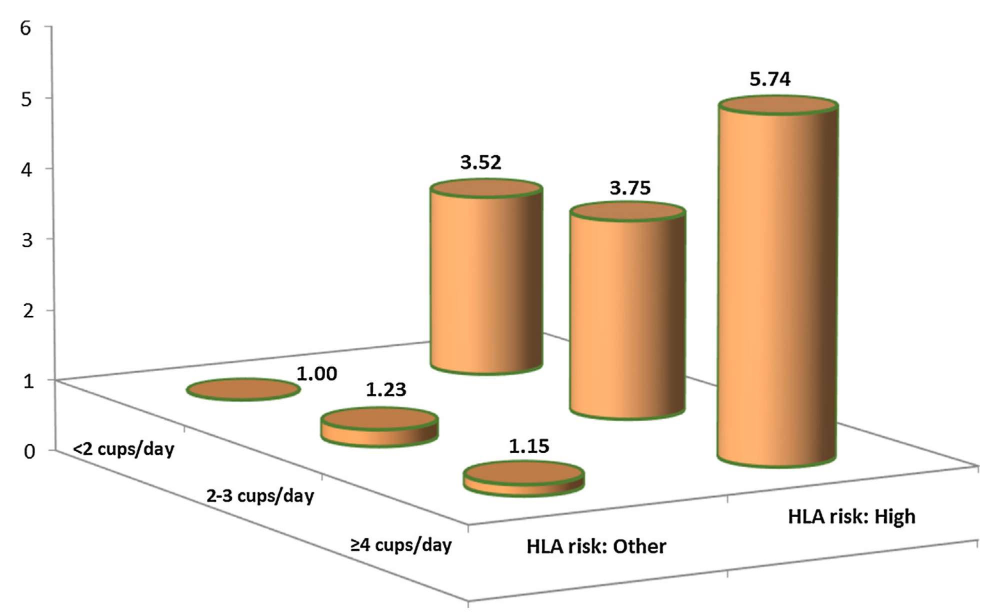

Fig. 1. Odds ratios (ORs) of latent autoimmune diabetes in adults (LADA) in relation to coffee consumption and human leucocyte antigen (HLA) risk genotypes. Data are conditioned on age and gender, and adjusted for smoking, body mass index, and levels of education and alcohol consumption. 'HLA risk: high' refers to genotypes DR4-DQ8, *DR3/4*, *DR3/3*, *DR4/4*, *DR4/3-DQ8* and *DQA1*0501-DQB1*0201*; 'HLA risk: Other' refers to genotypes *DR3/X*, *DR4/X*, *DR4-DQ7* and *DRX/X*.

between high HLA risk and heavy coffee consumption with an AP estimated as 0.36 (95% CI: 0.01–0.71; $P = 0.04370$; Table S6; see supplementary materials associated with this article online). Carriers of high-risk HLA genotypes and heavy coffee consumption had an OR of 11.78 (95% CI: 5.39–25.77) for $\text{LADA}_{\text{high}}$ and OR of 3.02 (95% CI: 1.52–6.01) for LADA_{low} (Fig. S1; see supplementary materials associated with this article online).

Coffee consumption, GADA, HOMA-IR and HOMA-β

On comparing median levels of HOMA indices, C-peptide and GADA across categories of coffee consumption in LADA and T2D patients (Table 3), it was noted that, in LADA, those with heavy coffee intakes had lower levels of C-peptide and β-cell function. In patients with T2D, levels of C-peptide and HOMA-IR were lower in heavy coffee drinkers, whereas no clear difference was seen in HOMA-β scores.

Sensitivity analysis

In an attempt to evaluate the potential influence of different time periods of recruitment into EIRA and ESTRID, an analysis was performed that was restricted to only those patients and controls recruited within the nearest time period of each other. This, which involved only small numbers (181 controls, 2008–2009; 51 LADA patients, 2009–2010), did not change the results (OR: 1.10 per cup/day, 95% CI: 0.88–1.38). A separate analysis of only women with high-risk HLA genotypes likewise produced similar results (OR: 1.12 per cup/day, 95% CI: 0.96–1.32).

Discussion

Our present study indicates that coffee consumption is positively associated with $\text{LADA}_{\text{high}}$ and that coffee intake interacts

Table 3
Median (interquartile range, IQR) values for homoeostasis model assessment of insulin resistance (HOMA-IR) and β-cell function (HOMA-β), C-peptide and glutamic acid decarboxylase antibodies (GADA) in patients with latent autoimmune diabetes in adults (LADA) and type 2 diabetes (T2D).

	Coffee consumption			P^a	P^b
	< 2 cups/day	2–3 cups/day	≥ 4 cups/day		
LADA					
Patients, *n*	108	192	184		
HOMA-IR, median (IQR)	3.0 (2.0–4.7)	2.7 (1.8–4.0)	2.7 (1.8–4.4)	0.2386	0.2731
HOMA-β, median (IQR)	43 (16–76)	47 (17–76)	26 (12–52)	0.0173	0.0026
C-peptide, median nmol/L (IQR)	0.83 (0.45–1.30)	0.73 (0.47–1.20)	0.63 (0.37–1.00)	0.0060	0.0117
GADA, median IU/mL (IQR)	177 (33–250)	203 (24–250)	250 (30–250)	0.2416	0.4186
T2D					
Patients, *n*	416	650	543		
HOMA-IR, median (IQR)	3.7 (2.9–5.0)	3.5 (2.6–4.8)	3.5 (2.7–4.7)	0.0352	0.0257
HOMA-β, median (IQR)	70 (43–96)	68 (45–93)	68 (41–93)	0.4805	0.7681
C-peptide, median nmol/L (IQR)	1.30 (1.00–1.60)	1.20 (0.95–1.60)	1.20 (0.94–1.50)	0.0013	0.0050

[a] Lowest vs. highest categories of coffee consumption.
[b] Across different categories of coffee consumption.

with HLA genotypes to promote LADA. It was also confirmed that coffee intake is inversely associated with T2D [1].

These findings are based on incident cases of diabetes recruited in Sweden between 2010 and 2017, and corroborate our previous results based on patients recruited during 2010–2013 from the same study [6]. Consistent with our results, Virtanen et al. [8] observed an increased risk of T1D in adolescents who consumed coffee regularly. While there do not appear to be any other studies of the association between drinking coffee and autoimmune diabetes, coffee consumption has been linked to an increased risk of rheumatoid arthritis [10]. One possible explanation for such an adverse effect of coffee could be the deleterious effects of some of its compounds, such as caffeine and other alkaloids, on pancreatic β cells as well as β-cell hyperstimulation, which might increase the risk of activating β-cell autoimmunity [7,8,38]. This notion is supported by our observation of poorer β-cell function (HOMA-β) in LADA with heavy coffee consumption. Another potential explanation is that exposure to coffee/caffeine might increase proinflammatory markers that promote autoimmunity [39]. In line with this hypothesis, our previous [6] and present findings indicate that coffee consumption is associated with $\mathrm{LADA_{high}}$ (the more autoimmune form of LADA), but not $\mathrm{LADA_{low}}$, which is more similar to T2D [6].

An additive interaction was also observed between coffee consumption and HLA risk genotypes associated with autoimmune diabetes. No previous study has examined the coffee–gene interaction in relation to autoimmune diabetes, although a strong interaction between high-risk HLA variants and heavy coffee intake has been found in rheumatoid arthritis [40]. However, the mechanisms underlying the observed interaction are not clear. The HLA risk genotypes [14,15] encoding antigens regulate autoimmune processes such as pathogenic T cells, which are involved in autoimmune destruction of pancreatic β cells [41]. The resultant triggering/exacerbation of autoimmune β-cell destruction by environmental factors (for example, coffee intake) might then be more pronounced in individuals carrying high-risk HLA variants. This may also indicate that coffee and HLA risk genotypes affect common biological pathways involved in the development of autoimmune diabetes. Taken together, these data suggest that the potential effects of coffee consumption may vary depending on the genetic characteristics of the individual. Elaboration of the precise mechanisms clearly require more investigation.

Nevertheless, studies have consistently shown that both caffeinated and decaffeinated coffee consumption is inversely related to T2D risk [1]. The reduced risk might be attributable to the beneficial effects of several compounds in coffee, such as caffeine, chlorogenic acid, magnesium and lignans with antioxidant properties [5], which might contribute to better glucose metabolism and insulin sensitivity [2,4]. In line with this idea is our observation that T2D patients with heavy coffee intakes are less insulin-resistant and have lower levels of C-peptide.

Strengths of the present study include the population-based design, large number of incident LADA cases, detailed information on coffee consumption and large number of potential confounders, including smoking, BMI, physical activity, total energy intake, alcohol consumption and level of education. However, information on coffee consumption was collected retrospectively, which may have introduced bias if patients changed their consumption after diagnosis and reported it accordingly. To minimize this problem, patients answered the questionnaire as soon after their diagnosis as possible and were instructed to report coffee consumption as it was prior to diagnosis. Importantly, the Swedish diabetes management guidelines include no recommendations regarding coffee consumption [42].

One study limitation was the use of controls recruited from another study (the EIRA). This was because no genetic information was available for controls collected from ESTRID. However, all controls were similar with regard to several characteristics, although the EIRA controls were slightly younger, and the proportion of women larger, compared with ESTRID controls. To account for this, they were matched with our patients by age and gender for the analyses [35]. Also, it is possible that some controls may have had undiagnosed diabetes (primarily T2D), which would have made them more similar to T2D cases in terms of coffee consumption prevalence, thereby leading to overestimation of the positive association between coffee consumption and LADA. Bias could also have been introduced if coffee consumption of the external controls did not reflect coffee consumption in the population generating the diabetes patients. However, it is noteworthy that the average daily coffee consumption in the ESTRID (2.9 cups/day) and EIRA controls (2.8 cups/day) was similar. Also, a similar positive association was found between coffee intake and LADA with high-risk HLA genotypes when internal controls from ESTRID were used. Nevertheless, the recruitment periods of EIRA (2005–2009) and ESTRID (2009–2016) differed and, if coffee consumption increased over time, this would have led to overestimation of the association with LADA. In fact, according to a report by the Swedish Board of Agriculture, coffee consumption has remained largely constant since 1976 [43]. More important, with regard to T2D, our results were consistent with those of numerous previous cohort studies, thereby supporting the validity of the study [1]. As information on family history of diabetes was unavailable for controls, this could not be taken into account. However, adjusting for family history of diabetes had little effect on the results of our previous report [6].

Conclusion

It appears that coffee intake is positively associated with LADA among carriers of high-risk HLA genotypes. Thus, the potential role of coffee in promoting autoimmunity warrants further investigation, given the widespread consumption of coffee.

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Authors' contributions

B.R. developed the objective of the study, analyzed the data and wrote the manuscript. S.C. researched the data (ESTRID), contributed to developing the objective of the study and interpretation of the results, and reviewed and revised the manuscript. T.A. contributed to the data analysis, and reviewed and revised the manuscript. L.G. and A.R. (ANDIS), P.-O.C. and M.M. (ANDIU) and L.A. (EIRA) contributed to the collection of data. L.G., L.A., A.W., T.T., M.M., A.R., E.A. and J.E.L. contributed to the discussion, interpretation of the results, and reviewed and revised the manuscript. All authors read and approved the final version of the manuscript. B.R. had access to all data in this study, and takes responsibility for the integrity of the data and accuracy of the data analysis.

Disclosure of interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data (Fig. S1, Tables S1–S6) associated with this article can be found, in the online version, at https://doi.org/10.1016/j.diabet.2018.05.002.

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